REMARKS

I. Pending claims

Claims 1-23 have been canceled and claims 33, 35-37, and 40-43 have been withdrawn from consideration. Claims 24-43 are being actively prosecuted. By this Response, claims 1-43 are canceled and substituted with new claims 44-60.

Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications.

II. Restriction Requirement

The Examiner maintained the restriction requirement and made it final with respect to the different proteins and polynucleotides claimed (Office Action of October 15, 2003, p. 2). The Examiner stated that the inventions listed in the different Groups do not relate to a single inventive concept because they lack the same or corresponding special technical feature with regard to a common structural property that would structurally distinguish them as a Group from the prior art (Office Action of October 15, 2003, p. 3).

Applicants do not agree with the Examiner. However, in order to expedite prosecution, The new claims do not include SEQ ID NO:1-2 and SEQ ID NO:4-5 or SEQ ID NO:6-7 and SEQ ID NO:9-10.

III. Rejoinder

Applicants thank the Examiner for acknowledging that if a product claim is held to be allowable, any claim to a process of using that product will be rejoined thereto (Office Action of October 15, 2003, p. 2). It is submitted that all the new method claims relate the product claims and are of the same scope, and should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b).

IV. Specification

The Examiner has stated that the application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). Applicants request that the Examiner add the abstract (infra p. 2) on a separate sheet as required by CFR 1.72(b).

V. Claim Rejections – 35 USC § 112, first paragraph, written description

The Examiner has rejected claims 24, 26, 29-31, 34, and 38 under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventions, at the time the application was filed, had possession of the claimed inventions. Specifically, the Examiner states that "the written description in this case only sets forth a polypeptide of SEQ ID NO:3 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to 'naturally occurring' protein variants of at least 90% identity to SEQ ID NO:3 as recited for example in claim 24(b)" (Office Action of October 15, 2003, p. 4).

Please note that the new claims contain a functional limitation for both the naturally occurring variants and for the biologically active fragments.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or

> disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met (footnotes omitted).

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:3 and SEQ ID NO:8 are specifically disclosed in the application (see, for example, pp. 3-6 of the Specification, and the Sequence Listing at pp. 2-3 and p. 8 of 21). Variants of SEQ ID NO:3 and SEQ ID NO:8 are described, for example, at pp. 3-4, and p.15. In particular, the preferred SEQ ID NO:3 variants (at least about 80%, more preferably at least about 90%, and most preferable at least about 95% amino acid sequence identity to SEQ ID NO:3) are described, for example, at pp. 16-17. SEQ ID NO:8 variants (at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to SEQ ID NO:8) are described, for example, at p. 17. Incyte clones in which the nucleic acids encoding the human CECRP-3 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1 and 4. Chemical and structural features of CECRP-3 are described, for example, in Table 2. Given SEQ ID NO:3, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:3 at least 90% identical to the amino acid sequence of SEQ ID NO:7. Given SEQ ID NO:8, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:8 at least 90% identical to the polynucleotide sequence of SEQ ID NO:8. The Specification describes (at Example III., p. 46, pp. 18-19, and Table 5) how to use BLAST and other methods to determine whether a given sequence falls within the "at least 90% identical" scope.

There is simply no requirement that the claims recite particular variant polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants are defined in terms of SEQ ID NO:3 ("An isolated polypeptide of. . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:3." The polynucleotide variants are defined in terms of SEQ ID NO:8 ("An isolated polynucleotide of . . . b) a polynucleotide comprising a

naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:8").

Because the recited polypeptide variants are defined in terms of SEQ ID NO:3, and the recited polynucleotide variants are defined in terms of SEQ ID NO:8, the precise chemical structure of every polypeptide variant and every polynucleotide variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For

example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of new independent Claims 44 and 51 recites chemical structure and functional limitation to define the claimed genus:

> 44. An isolated polypeptide of. . .
>
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:3, said polypeptide having cell cycle regulating activity,. . .
>
> 51. An isolated polynucleotide of. . . :
>
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:8. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides recited by the claims. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is highly variant

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variant. Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078); Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pp. 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., p. 6076.)

The present application is directed, *inter alia*, to CECRP proteins related to the amino acid sequence of SEQ ID NO:7. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as CECRP proteins and which have as little as 40% identity over at least

70 residues to SEQ ID NO:8. The "variant language" of the present claims recites, for example, an isolated polypeptide "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:3. . ." (note that SEQ ID NO:3 has 236 amino acid residues). This variation is far less than that of all potential CECRP proteins related to SEQ ID NO:8, i.e., those CECRP proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:8.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 8, 1998. Much has happened in the development of recombinant DNA technology in the 19 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:3 and SEQ ID NO:8, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants and the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they

differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:8. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides and polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Claim Rejections – 35 USC § 112, first paragraph, enablement

The Examiner has rejected claims 24, 26, 29-31, 34 and 38 under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed methods of detecting the recited polynucleotides and fragments thereof.

Applicants traverse the rejections on the following grounds:

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than **objective enablement**. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. Given the sequence

of SEQ ID NO:3, one of ordinary skill in the art could readily identify a polynucleotide encoding a polypeptide comprising a naturally occurring polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:3, using well known methods of sequence analysis without any undue experimentation. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, for example, p. 8, pp. 18-19, pp. 24-25, p. 39; and Example V at page 48. Thus, one skilled in the art need not make and test vast numbers of polynucleotides. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides that already exist in nature. The skilled artisan would also know how to use the claimed polynucleotides, for example in expression profiling, disease diagnosis, or detection of related sequences as discussed above. The specification also describes the expression vectors into which the claimed variants and fragments could be inserted, and the construction of fusion proteins (pp. 26-27 and Example XI at page 54).

Applicants respectfully point out that the claims of the instant application are drawn to **naturally occurring** variants. Thus it is not necessary to screen every conceivable variant which might be made using recombinant methods, as all that is claimed are those variant sequences which are found in nature. Through the process of natural selection, nature will have determined the appropriate sequences.

Furthermore, the claims are directed to polynucleotides, not polypeptides, and it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may be useful even if they encode defective CECRP polypeptides. For example, the variant polynucleotides could be used for the detection of sequences related to CECRP (see the specification, for example, at pages 38-39) including CECRP variants that may be associated with disease states, such as the diseases listed on pages 37-38 of the specification. See the specification at, for example, pages 39-43 for disclosure of how to use the claimed sequences in diagnostic assays.

Further, the Examiner requires working examples. There is no such requirement under the law

to provide "working examples." As set forth in *In re Borkowski,* 164 USPQ 642, 645 (CCPA 1970) (footnote omitted):

> However, as we have stated in a number of opinions, a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

See also M.P.E.P. 2164.02 as follows:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic"... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

Thus, there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to whether the specification provides a description of how to make what is claimed. The present specification provides the requisite description.

Contrary to the standard set forth in *Marzocchi* and *Borkowski*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established. For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

A. How to make

The Specification provides sufficient teaching of the manner and process of *making* the invention. SEQ ID NO:3 and SEQ ID NO:8 are specifically disclosed in the Specification (see, for example, the Sequence Listing and infra p. 10).

The making of the target polynucleotides of the claims by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 18, lines 27-30, page 19, line 13 through page 24, line 14, and page 31, lines 22-29. The making of the probes of the claims is disclosed in the Specification, e.g, at page 24, line 24 through page 25, line 7, page 37, lines 1-21, page 39, lines 20-27, page 40, line 16 through page 42, line 3, page 48, lines 23-33, and page 49, lines 9-30. This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

B. How to use

Applicants' invention is directed, *inter alia*, to polynucleotides encoding a protein having homology to a cell cycle regulation protein. The claimed polynucleotide have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of SEQ ID NO:3 (CECRP), for toxicology testing, and for drug discovery (Specification at, e.g., pp. 42-43). Further, as described in the Specification at pp. 16-17:

> In Table 1, columns 1 and 2 show the sequence identifiers for each of the amino acid and nucleic acid sequence, respectively. Column 3 shows the Clone ID of the Incyte Clone in which nucleic acids encoding each CECRP were first identified, and column 4, the cDNA library of this clone. Column 5 is entitled fragments, and shows the Incyte clones (and libraries) and shotgun sequences useful as fragments, for example, in hybridization technologies, and which are part of the consensus nucleotide sequence of each CECRP. The columns of Table 2 show various properties of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues; column 3, potential phosphorylation sites; column 4, potential glycosylation sites; column 5, identifying sequences and/or structural motifs; and column 6, analytical methods used to identify the protein through sequence homologies and protein motifs.
>
> The columns of Table 3 show the tissue expression of each nucleic acid sequence by Northern analysis, diseases or disorders associated with this tissue expression, and the vector into which each cDNA was cloned.
> The invention also encompasses CECRP variants. A preferred CECRP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the CECRP amino acid sequence, and which contains at least one functional or structural characteristic of CECRP.
> The invention also encompasses polynucleotides which encode CECRP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising the sequence selected from the group consisting of SEQ ID NO:6 through 10.
>
> The invention also encompasses a variant of a polynucleotide sequence encoding CECRP. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding CECRP. A particular aspect of the invention encompasses a variant of a nucleic acid sequence selected from the group consisting of SEQ ID NO:6 through 10 which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:6 through SEQ ID NO:10. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of CECRP.

VII. Claim Rejections – 35 USC § 112, second paragraph, indefiniteness

Claims 24-32, 34, and 38-39 have been rejected under 35 USC § 112, second paragraph, as being indefinite. Specifically, claims 24 and 34 are allegedly indefinite in the recitation of the phrase "naturally occurring." Applicants have removed this language from the claims.

Claim 21 is allegedly indefinite in the recitation of the phrase "biologically active fragment."

Although not acquiescing in the reasons for this rejection, the new claims contain a functional limitation for both the naturally occurring variants and for the biologically active fragments. Therefore, Applicants respectfully request reconsideration and withdrawal this rejection.

VIII. Claim Rejections – 35 U.S.C. §102(b)

Claims 24, 26 and 29 were rejected under 35 U.S.C. §102(b) for the reasons given at pages 8 and 9 of the Office Action.

Although not acquiescing in the reasons for this rejection, the new claims contain a functional limitation for both the naturally occurring variants and for the biologically active fragments. Therefore, Applicants respectfully request reconsideration and withdrawal this rejection.

VIII. Claim Rejections – 35 U.S.C. § 103

Claims 30, 31 and 38 were rejected under 35 U.S.C. §103 for the reasons given at pages 9 and 10 of the Office Action.

Although not acquiescing in the reasons for this rejection, the new claims contain a functional limitation for both the naturally occurring variants and for the biologically active fragments. Therefore, Applicants respectfully request reconsideration and withdrawal this rejection.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: 15 January 2004

James M. Verna, Ph.D.
Reg. No. 33,287
Direct Dial Telephone: (650) 845-5415

Customer No.: **27904**
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Attachments:

1) Results of BLAST search
2) Shimamoto et al reference and NCBI data sheet
3) Hsu et al reference and NCBI data sheet